Radiation Therapy of Cancer

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FEW BRANCHES of medicine have grown as rapidly and diversely as have all aspects of the science of radiology, radiobiology and the medical applications of nuclear science.

In commenting on the rapid growth of the use of ionizing radiation, Scott[8] said that "prior to World War II, all of the radium and radioactive materials in use in the entire world did not exceed three pounds." At present, tons of radioactive materials are being produced by thousands of workers in this new industry.

Andrews[1] defined the science and the art of clinical radiation therapy as the optimal combination of the variables of tissue susceptibility (radiosensitivity) and of the quantity, quality and time of irradiation and applying them to bring about a predictable clinical effect.

The value of radiation therapy is fully appreciated when it is realized that the only way cancer can be successfully controlled is by surgical operation, radium therapy or x-ray therapy, used singly or in combination. There is no scientific evidence to indicate that the incidence of cancer, in general, is decreasing. Some forms of cancer (for example, cancer of the stomach and uterus) are decreasing and others are increasing (leukemia, malignant lymphomas, for example). Cancer is the second most common cause of death from disease in children. Even if the causes and cure of cancer were discovered today, there would still be the need for radiation therapy for a considerable period.

One of the most important things to be considered in connection with radiation therapy of cancer is the damage that can be done by misdirected treatment or overtreatment and the tragedy that can ensue from less than optimal treatment. Therapeutic radiation should be planned, directed and carried out only by physicians thoroughly and particularly schooled and skilled in this method of treatment.

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Mode of Action of Ionizing Radiation

The primary objective of ionizing radiation is to destroy the malignant cells with as little damage as possible to the normal surrounding cellular structures. The major concern of the radiation therapist is with the amount of absorption of the beam of ionizing radiation which penetrates the tissues and not with that which passes through the body.

All cells are affected in some degree when exposed to ionizing energy. Fortunately, normal cells have a greater capacity to recover. All cells, both malignant and non-malignant, have varying degrees of radiosensitivity. The more radiosensitive the cells, the greater the response to ionizing energy. Radiosensitivity and radiocurability are not synonymous terms. A malignant tumor may be composed of highly radiosensitive cells but have a low curability factor.

Cells that are actively dividing, that are in high state of metabolic activity and that are less differentiated are usually the most radiosensitive. Highly radiosensitive tumors have the capacity to disseminate widely through vascular or lymphatic channels and to recur if inadequately treated.

Desjardins[3] has listed the relative radiosensitivity of the various body cells and tissues in the following decreasing order:

Lymphocytes
Granulocytes
Epithelial cells
Endothelial cells of the pleura, peritoneum, and blood vessels
Connective tissue cells
Muscle cells
Bone cells
Nerve cells

Even though some malignant tumors are considered to be relatively radioresistant, one cannot always predict what the radiation response will be until it is tried. However, radiation therapy should not be attempted in such cases unless it is either primarily the best form of therapy or other methods of therapy are no longer applicable. As a general rule, the first course of radiation therapy is most likely to produce the best results. Subsequent radiation is usually much less effective. Once a full course of radiation has been given, only under very special circumstances can adequate additional radiation be administered. There is a tolerance limit for all tissues, and excessive radiation therapy will produce complications of varying degrees of severity. Yet the radiation therapist must take certain calculated risks when treating radiocurable malignant tumors just as does the surgeon.

The Unit of Dose Measurement

The unit of measurement which is most familiar to physicians is the roentgen. When one roentgen of x-ray or gamma rays is passed through one milliliter of air, two billion ion pairs are formed. The definition of a roentgen is as follows: "One roentgen is an exposure dose of x-radiation or gamma radiation such that the associated corpuscular emission (electrons produced by the x or gamma rays) per 0.001293 gram of air produces, in air, ions carrying one electrostatic unit of quantity of electricity of either sign."

The unit which is coming into more general usage is the rad. The rad indicates the amount of absorbed energy and can be used for x-rays, gamma rays, neutrons and alpha and beta rays. One rad represents the absorption of 100 ergs of energy in one gram of matter. For practical purposes for the present ranges of radiation therapy, one roentgen is on the average equivalent to approximately 0.97 rad when the soft tissues are irradiated.

Tumor Dose

Radiation therapy doses should be reported to the referring physician as so many rads or roentgens delivered to the tumor in so many days, and the report should state the dates of the beginning and ending of the radiation therapy. To be more exact, the maximum tumor dose (delivered to the center of the tumor) and the minimum tumor dose (amount delivered to the periphery of the tumor) should be stated. Also to be made a part of the report is the type of equipment used and the half value layer (hvl). The term *half value layer* refers to the amount of absorber necessary to reduce the beam of ionizing energy by one-half as it emerges from the radiation source. Stating only the amount of the dose in air has very little meaning. The size, number and location of the treatment fields should be indicated, and any complications which may have occurred during radiation therapy.

Fractionation and Dose-Rate

A great deal of important research in radiobiology with respect to fractionation, dose-rate and cell survival has been done during the past ten years. The techniques for the study of the effects of irradiation on cells in vivo and in vitro have greatly increased our knowledge in radiobiology.

By *fractionation* is meant the distribution of the total tumor dose in two or more treatments over a period of weeks or, in some cases, months. Usually patients tolerate the radiation therapy much better when it is fractionated, and the margin of safety is also improved. Some therapists spread the fractionated treatment over a period of three months or more, but average time for the delivery of the total tumor dose for most deep-seated cancers is approximately five to six weeks (1000 to 1500 r or rads tumor dose per week). Much clinical research remains to be done to determine the optimal period of time and dose-rate for the delivery of a calculated tumor dose to each type of cancer.

The importance of adequate cellular oxygenation at the time of irradiation has been pointed out by Gray[4] and his associates. It has been estimated that hypoxic cells will require between two and three times the dose of radiation to destroy them that adequately oxygenated cells do.

In 1954, Churchill-Davidson and coworkers[2] began a clinical trial of irradiating patients with advanced cancer while they were breathing oxygen at 3 and later at 4 atmospheres of absolute pressure. Their results have encouraged them to continue this important experimental study. In 1961 Mallams and coworkers began the use of hydrogen peroxide as a source of oxygen in a regional intra-arterial infusion system in the treatment of patients with advanced cancer in an attempt to improve the end results.

Sambrook[7] uses a split course method of radiation therapy. Using this technique, he has never seen clinical evidence of renewed growth of a tumor in under six to eight weeks after a dose of approximately 2,500 r has been given in two weeks. The split course method with the interposition of a four-week rest period gives the patient a complete respite during the course of treatments and also spares to some extent the normal tissues and permits normal recovery to begin.

The results of the numerous current studies, both clinical and experimental, concerning the dose-time relationship should certainly facilitate improvement in radiation treatment methods.

Cure or Palliation

Before proceeding with radiation therapy, it must be determined whether cure is possible by this method, or only palliation can be achieved. Biopsy confirmation of the type of tumor, if at all possible, should be obtained. The cell type will indicate to a large extent the radiosensitivity of the tumor. The extent of the disease—whether localized, confined to the regional lymph nodes or disseminated—is of great importance in determining the prognosis and the amount of radiation therapy required. Further considerations are the anatomic location of the tumor, whether or not the patient is in good condition, the presence or absence of sepsis, the status of the hematopoietic system and the patient's mental outlook. In other words, the patient's general status is evaluated as well as the tumor.

It is unfortunate that diagnostic methods are not available which will clearly indicate the exact extent of a cancer. Clinically and radiographically the cancer may appear to be localized when, in fact, dissemination may have occurred but has not become detectable. Many operations would be eliminated and treatment planning could be more appropriately done if the exact anatomic stage or extent of the disease could be determined.

Once it has been decided to give a course of therapy, consideration should be given to whether or not other modalities should be combined with it. A method of therapy should not be decided upon merely because the physician in charge of the case has had experience with only one type of therapy—the method should be the best for the particular patient regardless of who is going to do it.

If only palliation is the objective, then again it should be decided whether it should be by surgical operation, by radiation, by hormone, steroid or chemotherapy, or by a combination of means and methods. There are definite indications for the use of each of the various methods for providing relief for the patient.

Relief of symptoms such as pain, hemorrhage, intractable cough, inability to swallow, intestinal obstruction secondary to tumor, edema such as is produced by lung carcinomas with an associated superior vena caval syndrome, pathological fracture, spinal cord compression, varying degrees of paralysis secondary to brain metastasis from breast or lung—these are some of the conditions for which palliative radiation can be effective.

No other method of therapy has ever produced more consistent palliation in a greater number of cases of various types of cancer with less mortality and morbidity than has radiation.

If a patient has widespread disease such as is present with many malignant lymphomas, aggressive therapy must not be done. The patient should not be made more uncomfortable by too vigorous therapy in the presence of hopeless disseminated disease. It is essential that the radiation therapist have excellent training and wide experience because he will frequently need to combine other methods of therapy with radiation at some time during the course of the management of patients with far advanced disease. The successful management of the patient with cancer requires teamwork and the radiation therapist must collaborate with the patient's referring physician.

Radiation—Equipment and Sources[9]

- Contact x-ray therapy (40-60 kv)
- Superficial x-ray therapy (60-140 kv)
- Intermediate or medium voltage therapy (140-185 kv)
- High voltage orthodox, conventional, deep x-ray therapy (200-300 kv)
- Supervoltage therapy (400-1,000 kv)
  - Cesium 137 teletherapy
- Megavoltage therapy
  - X-rays generated by the one and two million volt GE alternating current resonance transformer and the two Mev. Van de Graaff constant potential electrostatic generator
    - Gamma ray teletherapy using from 10-50 gram radium packs
    - Cobalt 60 teletherapy
    - Linear accelerator 4-50 Mev. electrons or x-rays
    - Betatrons: electrons or x-rays
    - Cyclotron: protons, deutrons, alpha particles
    - Synchro-cyclotron: protons, deuterons, alpha particles
    - Synchrotron: electrons
    - Proton synchrotron, Bevatron, Cosmotron } Protons
- Interstitial and/or intracavitary therapy
  - Radium, radon seeds, cobalt^{60}, tantalum^{182}, and iridium ^{192}
- Systemic sources
  - Iodine^{131}, and phosphorus ^{32}
- Intracavitary use (pleural and peritoneal cavities)
  - Radioactive gold^{198} and phosphorus^{32}

Radioactive isotopes administered internally or placed in the pleural or peritoneal cavities play a very minor role in cancer therapy. Iodine-131 (beta and gamma rays) is of value in the treatment of some thyroid cancers with disseminated disease and Phosphorus-32 (beta particles) is useful in the treatment of chronic leukemia and polycythemia rubra vera. Intracavitary administration of radioactive gold-198 (beta and gamma rays) may help prevent ascites or pleural effusion. Strontium-90 (pure beta emitter) is used in certain benign and malignant ophthalmic conditions. Cobalt-60, iridium-192, radium-226 and tantalum-182 are gamma emitters and may be employed interstitially when encapsuled in needles or tubes. Cobalt-60 and cesium-137 when used in large quantities at a distance (teletherapy) may be just as effective as high energy x-rays. Radium "bombs" or "packs" (a large quantity of radium, 10 to 50 grams) have been used in the treatment of cancer. Since cobalt-60 and cesium-137 are so much cheaper and more plentiful, these radioactive elements have replaced radium when used in this manner.

Radiation may be electromagnetic, such as x-rays or gamma rays, or particulate radiation—for example, alpha particles, beta particles, protons, neutrons, deuterons or electrons.

The only difference between gamma rays and x-rays is that gamma rays are emitted by radioactive sources such as radium and radioactive cobalt-60. X-rays are produced by certain types of electrically controlled units. Electromagnetic radiation travels with the speed of light and has the ability to penetrate the tissues of the body and other substances. Alpha particles have little penetrating power; even a sheet of paper will stop them. If alpha emitting isotopes are absorbed within the body, considerable harm may result. Beta particles or electrons have a penetrating power which is dependent upon their energy. They are exceedingly light in weight. Neutrons do not have an electrical charge. With fast neutrons, the ionizing particle is the recoil proton which it produces. Protons carry a positive charge and are used largely in nuclear research.

The biological effects of radiation are dependent upon whether radiation is given to the whole body in a single dose (total body radiation) or is given in repeated doses to a limited area as when it is delivered to a certain area of the body in a specified period in the treatment of cancer.

Megavoltage Therapy

Although megavoltage therapy was introduced over thirty years ago, there was no widespread interest or use of this modality until cobalt-60 became available in 1951.

Cobalt-60 equipment and radiation sources could be obtained at considerably less cost and required much less space than some of the existing megavoltage units. The obvious advantages of megavoltage therapy, especially for the treatment of deep seated cancers, caused surgeons, urologists and other specialists to take renewed interest in the use of radiation therapy.

Megavolt means million volts. However, the words *supervoltage* and *megavoltage* have been used interchangeably to indicate one million or more electron volts of energy. Although cesium-137 sometimes is described as megavoltage equipment, it does not really qualify since its maximum energy is 661 kilovolts. It is not believed that this source of radiation will ever be widely used because of its penumbra and low output, in spite of its long half life (28 years).

The development of megavoltage equipment has not eliminated the use of superficial and conventional (orthovoltage, deep x-ray) x-ray therapy, nor was it ever intended to do so.

For any specialty to make progress, constant efforts must be made to perfect existing equipment or to develop new equipment and to improve present techniques. This is precisely the role of megavoltage therapy.

The physical advantages or qualities of megavoltage therapy as compared with conventional x-ray therapy (200-300 kv) in the treatment of cancer are as follows:

1. Maximum point of ionization (100 per cent dose) is located several millimeters beneath the skin, depending upon the energy of the radiation used. This results in skin-sparing and in more comfort for the patient. Since little or no skin reaction is produced even with large total doses, the radiation therapist must be experienced in its use in order not to deliver excessive doses to deep-seated tissues. The maximum effect is produced in the subcutaneous tissues or superficial layers of the fascia or muscles depending upon the energy of the radiant beam.

2. With the linear accelerators, betatrons and newer cobalt sources, it is possible to deliver a large tumor dose from target or source distances of from 80 to 100 cm from the skin.

3. There is considerable improvement in the depth dose when deep-seated tumors are treated. For example, with 250 kv equipment, a hvl 2.5 mm of copper and target skin distance of 50 cm, the depth dose delivered to 10 cm is approximately 40 per cent; for the 6 Mev. linear accelerator with target skin distance of 100 cm the depth dose delivered at 10 cm is 68 per cent.

4. Large fields can be irradiated. When "beam shaping" devices are used, treatment fields of any

size or configuration can be planned and provision made for protection of the tissues in the areas that are not to be irradiated. This may be very important when, as in certain cases of malignant lymphoma, one wishes to treat both sides of the neck both axillae and the mediastinum with one field, yet protect intervening tissues.

5. With more precise definition of the radiation beam and less side scatter, the volume of tissue irradiated is reduced. As a result of this and the skin-sparing effect, less radiation sickness occurs in the majority of patients.

6. The differential absorption between bone and the soft tissues is decreased, providing for more homogeneous dosage. There is less tendency for development of necrosis of cartilage or bone. Cancers located in the head and neck and in the pelvic regions can be more uniformly radiated and the tumor dose more precisely determined because of the increased uniformity of absorption of the ionizing radiation.

The place of megavoltage in cancer therapy has been clearly established. The mere fact that results as good as those obtainable by conventional x-ray therapy can be achieved with it is not enough to warrant its use. But an increasing number of scientific reports indicating an improved five-year survival for patients with certain types of tumor following the use of megavoltage therapy, and other factors such as ease of administration and tolerance by the patient, certainly indicate that all well-equipped radiation therapy treatments centers should have some type of megavoltage equipment available.

The major uses of megavoltage therapy will be in the treatment of cancer in the head and neck, the esophagus, brain, lungs, bladder and ovaries. It also is useful in certain other types of intra-abdominal, retroperitoneal and intrathoracic tumors.

The major interest in radiation therapy and in new therapeutic agents during the past 15 years has been in:

1. Equipment
   a. Improved cobalt-60 sources and equipment
   b. The potential therapeutic uses of cesium 137
   c. Electron beam therapy (4-70 Mev.)
   d. Neutron, proton and meson sources
   e. Improved radioisotope diagnostic techniques to determine precise tumor extent and localization
2. Radiobiology
   a. Use of tissue cultures and other methods to increase knowledge of the possible explanation for the differences in radiosensitivity of the different types of tumor cells
   b. A reevaluation of the significance of relationship of time-dose in radiation therapy
   c. The need for precise knowledge of the metabolism of malignant cells

3. The use of preoperative radiation in the treatment of lung, bladder and breast cancer and of other malignant tumors.

4. The role of chemotherapy and particularly when combinations of surgical operation, chemotherapy and radiation therapy are indicated.

5. Teamwork is essential among the various specialists treating cancer in order that the patient may obtain the best possible therapeutic result.

6. The long overdue need for radiation therapy to take its proper place as one of the only two known methods by which cancer can be cured. This will only come about through complete reorganization of the teaching program for medical students and in the training of residents. Little or no information is given to medical students about radiation therapy and radiobiology. The training of the general radiologist is often meager with regard to radiation therapy.

Eventually, adequately staffed radiation therapy centers will have to be established because of the enormous initial cost and maintenance of a well-equipped therapy center.

Can Radiation Be Curative?

Can radiation therapy be curative? In some circumstances and at some sites the radiation therapist can produce curative results.

A few of the special types of cancer that can be successfully controlled by radiation therapy are basal cell and squamous cell carcinomas of the skin; seminoma and dysgerminoma; malignant lymphomas; carcinomas of the tonsil, of the oral cavity and of the larynx when limited to one vocal cord and the cord is movable; and carcinoma of the anus.

Radiation therapy can be very effective when combined with surgical operation in the treatment of carcinoma of the breast and urinary bladder, Wilms' tumors, metastatic carcinoma to lymph nodes, and when given preoperatively for lung and rectal carcinomas.

Approximately 65 per cent of all patients with cancer at some time or other in the course of their disease will be seen by the radiologist. No other single modality can be as effective when given for palliation. In a high percentage of localized cancer, excellent five-year survival results can be achieved by adequate radiation.

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